^{17}O-NMR, EPR and NMRD Characterization of [Gd(DTPA-BMEA)(H_2O)]: A Neutral MRI Contrast Agent

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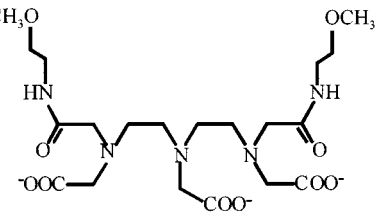
A study including variable-temperature and -pressure, multiple-field ^{17}O NMR, EPR and NMRD has been performed on the MRI contrast agent, [Gd(DTPA-BMEA)(H_2O)]. The water exchange rate [$k_{ex}^{298} = (0.39 \pm 0.02) \times 10^6$ s^{-1}] and the activation volume ($\Delta V^{\neq} = +7.4 \pm 0.4$ cm^3 mol^{-1}), hence the mechanism, are identical to those for [Gd(DTPA-BMA)(H_2O)]. The longer rotational correlation time of [Gd(DTPA-BMEA)(H_2O)], as obtained from a global analysis of ^{17}O-NMR, EPR and NMRD data, and compared to that of [Gd(DTPA-BMA)(H_2O)], can be explained by water molecules hydrogen-bonded to the ether oxygen atoms of the ligand side chain.

Application of paramagnetic complexes of Gd^{3+} for contrast enhancement in clinical Magnetic Resonance Imaging (MRI) is now routine.[1] The first-generation contrast agents approved were ionic chelates, $[Gd(DTPA)(H_2O)]^{2-}$ (in Magnevist™)[2][3] and $[Gd(DOTA)(H_2O)]^-$ (in Dotarem™).[3][4] The search for low osmolar, highly hydrophilic agents that can be administered at higher doses with fewer adverse side effects has led to the development of several neutral agents, such as [Gd(DTPA-BMA)(H_2O)] (in Omniscan™),[3][5] [Gd(HP-DO3A)(H_2O)] (in ProHance™)[3] or [Gd(DTPA-BMEA)(H_2O)] (in OptiMARK®) (Scheme 1).[6–11]

Scheme 1. Structure of the ligand 1,7-bis[(*N*-methoxyethylcarbamoyl)methyl]-1,4,7-tris(carboxymethyl)-1,4,7-triazaheptane (DTPA-BMEA)



The proton relaxation enhancement due to presence of the contrast agent is expressed as proton relaxivity and depends on several factors, for example the rates of water exchange, molecular rotation, and electronic relaxation. In principle, measurement of the variation of proton relaxivity as a function of the magnetic field strength, the nuclear magnetic relaxation dispersion (or NMRD) profile, provides information on all of these parameters. In reality, the separation of the contributions of water exchange, rotation and electronic relaxation to the measured relaxivity is difficult, thus it is necessary to determine these parameters by independent methods. Water exchange rates can be directly obtained by ^{17}O-NMR measurements, whereas EPR experiments yield electronic relaxation rates. Here we report a variable temperature and pressure, multiple field ^{17}O-NMR experiment together with an EPR and NMRD study on [Gd(DTPA-BMEA)(H_2O)]. Analysis of these experiments provided the parameters describing water exchange, rotation and electronic relaxation. Certainly, the real effectiveness of the complex as a contrast agent needs to be tested in tissues or tissue-like models, as the complex-protein interactions may affect the paramagnetic enhancement in vivo.[12–14]

Results and Discussion

UV/Vis spectra were obtained of the analogous europium complex, [Eu(DTPA-BMEA)(H_2O)], in the range of $579 < \lambda < 581$ nm, and yielded a single absorption band that was invariant between 0 and 90°C. The $^7F_o \rightarrow {}^5D_0$ transition band of the Eu^{3+} ion that occurs in this region is very sensitive to changes in the coordination environment of the metal ion.[15] Therefore, the invariance of the spectrum excludes any equilibrium between differently hydrated species, i. e. the only species present is the europium complex with one inner sphere water molecule. Since Gd is very similar to Eu, this finding could be extended to the Gd^{III} complex as well. This is also supported by the value of the ^{17}O scalar coupling constant, $A/\hbar$, which is in the usual range for Gd^{III} complexes with one water molecule in the first coordination sphere (Table 1).[16]

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjic or from the author.

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Table 1. Parameters obtained from the simultaneous fit of ^{17}O-NMR, EPR and NMRD data; the parameters in parenthesis were obtained by fitting only ^{17}O-NMR and EPR data; the values in italics were fixed in the fitting procedure

	DTPA[16]	DTPA-BMA[16]	DTPA-BMEA
$k_{ex}^{298}/10^6$ s^{-1}	3.3 ± 0.2 (4.1 ± 0.3)	0.45 ± 0.01 (0.43 ± 0.02)	0.39 ± 0.02 (0.37 ± 0.02)
$\Delta H^{\neq}$/kJ mol^{-1}	51.6 ± 1.4 (52.0 ± 1.4)	47.6 ± 1 (46.6 ± 1)	49.8 ± 1.4 (49.1 ± 2)
$\Delta S^{\neq}$/J mol^{-1}K^{-1}	+53 ± 5 (+56 ± 5)	+22.9 ± 3.6 (+18.9 ± 4)	+27 ± 6 (+26 ± 6)
$\Delta V^{\neq}$/cm^3 mol^{-1}	+12.5 ± 0.2	+7.3 ± 0.2	+7.4 ± 0.4
A/h/10^6 rad s^{-1}	−3.8 ± 0.2 (−3.8 ± 0.2)	−3.8 ± 0.2 (−3.6 ± 0.3)	−4.1 ± 0.4 (−4.1 ± 0.4)
τ_R^{298}/ps	58 ± 11 (103 ± 10)	66 ± 11 (167 ± 5)	93 ± 4 (172 ± 12)
E_R/kJ mol^{-1}	17.3 ±0.8 (18 ± 2)	21.9 ± 0.5 (21.6 ± 0.1)	24.5 ± 1 (23.4 ± 1)
τ_v^{298}/ps	25 ± 1 (0.25 ± 0.01)	25 ± 1 (34 ± 8)	20.3 ± 0.8 (32 ± 8)
E_v/kJ mol^{-1}	1.6 ± 1.8 (1.6 ± 1.8)	3.9 ± 1.4 (9 ± 2)	*3.9 (3.9)*
$\Delta^2/10^{20}$ s^{-2}	0.46 ± 0.02 (0.15 ± 0.02)	0.41 ± 0.02 (0.38 ± 0.02)	0.48 ± 0.02 (0.52 ± 0.04)
$D_{GdH}^{298}/10^{-10}$ m^2 s^{-1}	20 ± 3	23 ± 2	26 ± 1
E_{GdH}/kJ mol^{-1}	19.4 ± 1.8	12.9 ± 2.1	15.3 ± 0.5
$\chi(1+\eta^{2/3})^{1/2}$/MHz	*7.58*/14 ± 2	*7.58*/18 ± 2	*7.58*/15.0 ± 0.1
r_{GdO}/A	2.20 ± 0.09/*2.5*	2.12 ± 0.04/*2.5*	2.17 ± 0.02/*2.5*

^{17}O NMR, EPR and NMRD

The variable-temperature ^{17}O-NMR, EPR and NMRD data were analysed in a simultaneous fitting procedure, which is based on the several parameters that are common to these techniques (all relevant equations are given in the Appendix). Details of this approach have been previously described.[16] A variable-pressure ^{17}O-NMR study permitted determination of the activation volume for the water exchange process. The resulting curves are shown in Figures 1 and 2 and the fitted parameters are given and compared to those of other Gd^{III}-based contrast agents in Table 1.

Water Exchange

The rate (k_{ex}^{298}) and the activation volume ($\Delta V^{\neq}$), thus the mechanism of the water exchange, are identical for the two bisamide complexes, [Gd(DTPA-BMEA)(H_2O)] and [Gd(DTPA-BMA)(H_2O)]. This is a general finding based on several monomer, dimer or polymer Gd^{III} complexes, i.e. the water exchange rate is not affected by structural changes outside the inner coordination sphere.[17−20] As compared to [Gd(DTPA)(H_2O)]$^{2-}$, the exchange rate is about one order of magnitude lower for the bisamide complexes, whereas the exchange mechanism remains dissociative interchange. The decrease in the exchange rate was explained in terms of a decreased steric crowding around the metal ion when carboxylates are replaced by amide groups.[19] In dissociative interchange processes, high steric crowding helps bond breaking. This effect is less important for amide complexes, which results in a slower water exchange compared to the corresponding carboxylates.

Electronic Relaxation

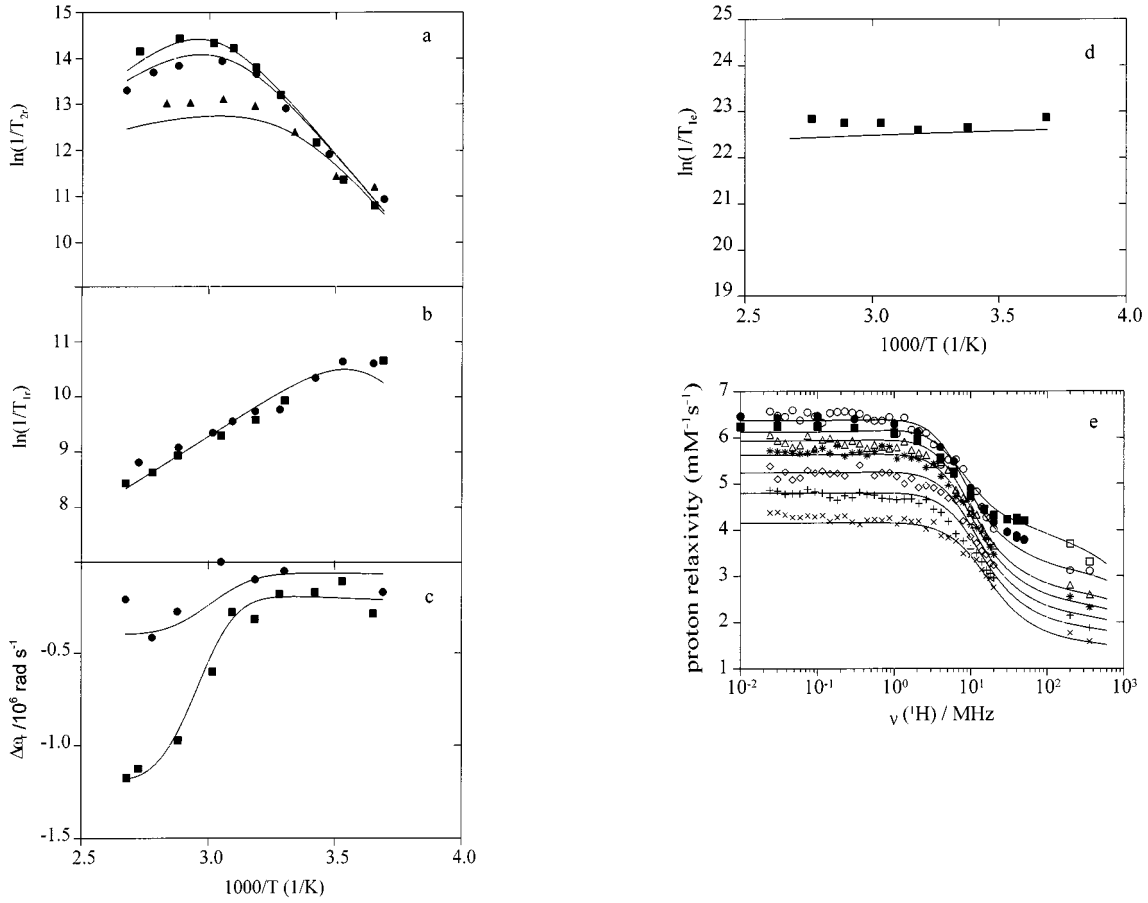
The parameters describing electronic relaxation (the mean square zero-field splitting energy, Δ^2, and the correlation time for the modulation of the zero-field splitting, τ_v^{298}) are identical for the [Gd(DTPA-BMA)(H_2O)] and [Gd(DTPA-BMEA)(H_2O)] complexes.

Rotation

The rotational correlation time is determined by the longitudinal ^{17}O relaxation rates and by the ^{1}H-NMRD data. Both methods have the same drawback as far as the absolute value of τ_R is concerned, i. e. reliance on distance estimates (Gd−H distance for NMRD, or the Gd−O distance for ^{17}O NMR), which have a strong influence on the absolute value of τ_R. In NMRD, the outer sphere contribution to relaxivity is also important, whereas in ^{17}O NMR it is negligible.[21] Due to the practical importance of NMRD data for MRI, contrast agents are generally characterized by the rotational correlation times as obtained from NMRD. In the simultaneous treatment of NMRD and ^{17}O-NMR data a single τ_R is fitted, which we attribute to the rotation of the Gd−water vector. There is very often a discrepancy between the τ_R values obtained in separate fits of ^{17}O- and ^{1}H-NMR data (τ_R from ^{17}O NMR is much longer), due to the use of the incompatible Gd−H and Gd−O distances. In the simultaneous treatment we allow for this by fitting either the Gd−oxygen(water) distance (r_{GdO}) or the quadrupolar coupling constant [$\chi(1 + \eta^2/3)^{1/2}$], which practically means that the rotational correlation time obtained in this way is determined only by the proton relaxation rates.[16]

The rotational correlation time for [Gd(DTPA-BMEA)(H_2O)], as obtained from the simultaneous fit, τ_R^{298} = 93 ps, is longer than the one for [Gd(DTPA-BMA)(H_2O)] (66 ps). This increase is larger than what would correspond to the increase in the molecular weight. A reasonable explanation can be that there are water molecules hydrogen-bonded to the ether oxygen atoms of the DTPA-BMEA side chains, a situation that may slow down the rotation of the complex. This seems to be also supported by the higher value of the diffusion constant obtained for [Gd(DTPA-BMEA)(H_2O)], as compared to [Gd(DTPA-BMA)(H_2O)] or [Gd(DTPA)(H_2O)]$^{2-}$. It should be noted, however, that the rotational correlation times obtained from ^{17}O longitudinal relaxation rates (by fixing the Gd−O distance to 2.5 Å and the quadrupolar coupling constant to 7.58 MHz) are very similar for the two bisamide complexes {167 and 172

Figure 1. Temperature dependence of reduced transverse (a), longitudinal (b) ^{17}O-relaxation rates and chemical shifts (c) at B = 14.1 T (■), 4.7 T (●) and 1.41 T (▲); transverse electronic relaxation rates (d) and NMRD profiles (e) at T = 5°C (□, ■), 35°C (○, ●), 43°C (▲), 48°C (*), 53°C (◇), 60°C (+) and 70°C (×) (■ and ● obtained from Seymour Koenig, 360- and 600-MHz data with Bruker spectrometers, otherwise with Stelar FFC relaxometer); the lines represent the simultaneous least-squares fit to all data points as described in the text



ps for [Gd(DTPA-BMA)(H_2O)] and [Gd(DTPA-BMEA)-(H_2O)], respectively}.

Conclusion

The complexes [Gd(DTPA-BMA)(H_2O)] and [Gd-(DTPA-BMEA)(H_2O)] are identical in respect to water exchange and electronic relaxation. The rotational correlation time for [Gd(DTPA-BMEA)(H_2O)] appears to be longer according to the global analysis of ^{17}O-NMR, EPR and NMRD data, probably due to hydrogen-bonded water molecules around the ether oxygen atoms of the ligand.

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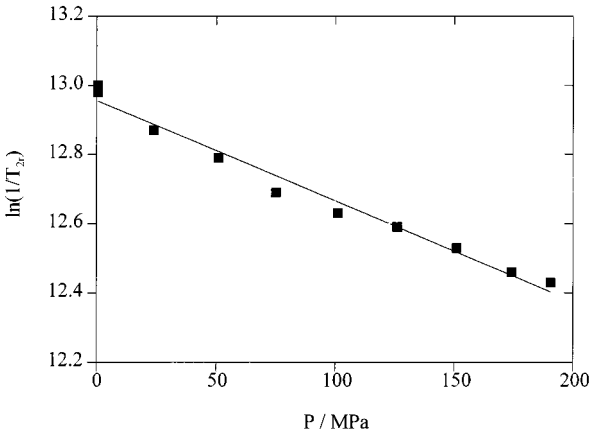
Figure 2. Pressure dependence of reduced transverse ^{17}O relaxation rates of [Gd(DTPA-BMEA)(H_2O)] at 298.2 K and B = 9.4 T; the line represents the least-squares fit that yields an activation volume of $\Delta V^{\neq}$ = +(7.4 ± 0.4) cm^3 mol^{-1}



Experimental Section

General: [Gd(DTPA-BMEA)(H_2O)] was obtained from Mallinckrodt Inc.[22] For the ^{17}O-NMR measurements, solutions of 44

mmol/kg (pH = 5.1) and 118 mmol/kg (pH = 4.7) were used. To improve the sensitivity, ^{17}O-enriched water (10% $H_2{}^{17}O$, Yeda R& D Co., Israel) was added to the Gd complex solutions to yield in 2% ^{17}O enrichment. A 44 mmol/kg solution was used for the EPR study. The absence of free Gd^{3+} ions in all solutions was verified by using xylenol orange indicator.[23] The [Eu(DTPA-BMEA)] solution (0.169 M) was prepared by adding an equimolar quantity of the ligand to a $Eu(ClO_4)_3$ solution and adjusting the pH to 4.7. − The UV/Vis measurements were performed in thermostated cells with a 10-cm optical path length in a Perkin-Elmer Lambda 19 spectrophotometer. − Transverse and longitudinal ^{17}O relaxation rates and chemical shifts were measured at three different magnetic fields using Bruker spectrometers: AMX2-600, 14.1 T, 81.4 MHz; AC-200, 4.7 T, 27.1 MHz; and a 1.41-T 8.14-MHz electromagnet connected to an AC-200 console. The technique used for the ^{17}O-NMR measurements has been described previously.[24] − The EPR spectra were recorded at X-band (0.34 T) using a Bruker ESP 300E spectrometer. − The $1/T_1$ NMRD profiles were obtained with a field-cycling relaxometer in the Department of Neurosurgery, The New York Medical College, Valhalla, NY,[25][26] or with a Stelar Spinmaster FFC relaxometer, in Lausanne ([Gd] = 1−2 mM). − High-field NMRD values (360 MHz and 600 MHz) were measured with Bruker spectrometers.

Data Analysis: The least-squares fitting was performed with Scientist® for Windows™ by Micromath®, version 2.0. The reported errors correspond to one standard deviation obtained by the statistical analysis.

Appendix

Oxygen-17 NMR: From the measured ^{17}O-NMR relaxation rates and angular frequencies of the paramagnetic solutions, $1/T_1$, $1/T_2$ and ω, and of the acidified water reference, $1/T_{1A}$, $1/T_{2A}$ and ω_A, one can calculate the reduced relaxation rates and chemical shift, $1/T_{1r}$, $1/T_{2r}$ and $\Delta\omega_r$, which may be written as in Eqs. 1−3[27], where $1/T_{1m}$, $1/T_{2m}$ are the relaxation rates of the bound water, $\Delta\omega_m$ is the chemical shift difference between bound and bulk water.1

$$\frac{1}{T_{1r}} = \frac{1}{P_m}\left[\frac{1}{T_1} - \frac{1}{T_{1A}}\right] = \frac{1}{T_{1m} + \tau_m} \tag{1}$$

$$\frac{1}{T_{2r}} = \frac{1}{P_m}\left[\frac{1}{T_2} - \frac{1}{T_{2A}}\right] = \frac{1}{\tau_m}\frac{T_{2m}^{-2} + \tau_m^{-1}T_{2m}^{-1} + \Delta\omega_m^2}{(\tau_m^{-1} + T_{2m}^{-1})^2 + \Delta\omega_m^2} \tag{2}$$

$$\Delta\omega_r = \frac{1}{P_m}(\omega - \omega_A) = \frac{\Delta\omega_m}{(1+\tau_m T_{2m}^{-1})^2 + \tau_m^2\Delta\omega_m^2} + \Delta\omega_{os} \tag{3}$$

$\Delta\omega_m$ is determined by the scalar coupling constant, $A/\hbar$, according to Eq. 4, where B represents the magnetic field.

$$\Delta\omega_m = \frac{g_L\mu_B S(S+1)B}{3k_B T}\frac{A}{\hbar} \tag{4}$$

The outer-sphere contribution to the ^{17}O chemical shift is proportional to $\Delta\omega_m$, where C_{os} is an empirical constant (Eq. 5).

$$\Delta\omega_{0S} = C_{0S}\Delta\omega_m \tag{5}$$

The ^{17}O longitudinal relaxation rates are given by Eq. 6[28], where γ_S is the electron and γ_I is the nuclear gyromagnetic ratio (γ_S = 1.76×10^{11} rad s^{-1} T^{-1}, $\gamma_I = -3.626 \times 10^7$ rad s^{-1} T^{-1}), r is the effective distance between the electron charge and the ^{17}O nucleus, I is the nuclear spin (5/2 for ^{17}O), χ is the quadrupolar coupling constant and η is an asymmetry parameter:

$$\frac{1}{T_{1m}} = \left[\frac{1}{15}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\hbar^2\gamma_I^2\gamma_S^2}{r_{GdO}^6}S(S+1)\right]\times\left[6\tau_{d1} + 14\frac{\tau_{d2}}{1+\omega_S^2\tau_{d2}^2}\right] + \frac{3\pi^2}{10}\frac{2I+3}{I^2(2I-1)}\chi^2(1+\eta^2/3)\tau_R \tag{6}$$

$$\tau_R = \tau_R^{298}\exp\left[\frac{E_R}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right] \tag{7}$$

In the transverse relaxation the scalar contribution, $1/T_{2sc}$, is the most important one (Eq. 8)[21]. In Eq. 8, $1/\tau_{sj}$ is the sum of the exchange rate constant and the electron spin relaxation rate.

$$\frac{1}{T_{2m}} \cong \frac{1}{T_{2sc}} = \frac{S(S+1)}{3}\left(\frac{A}{\hbar}\right)^2\left(\tau_{s1} + \frac{\tau_{s2}}{1+\omega_s^2\tau_{s2}^2}\right) \tag{8}$$

$$\frac{1}{\tau_{sj}} = \frac{1}{\tau_m} + \frac{1}{T_{je}} \qquad j = 1,2$$

The binding time (or exchange rate, k_{ex}) of water molecules in the inner sphere is assumed to obey the Eyring equation (Eq. 9), where $\Delta S^{\neq}$ and $\Delta H^{\neq}$ are the entropy and enthalpy of activation for the exchange process, and $k_{ex}{}^{298}$ is the exchange rate at 298.15 K.

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_B T}{h}\exp\left\{\frac{\Delta S^{\neq}}{R} - \frac{\Delta H^{\neq}}{RT}\right\} = \frac{k_{ex}^{298}T}{298.15}\exp\left\{\frac{\Delta H^{\neq}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \tag{9}$$

EPR: The ZFS terms can be expressed by Eqs. 10 and 11[29][30], where Δ^2 is the trace of the square of the transient zero-field-splitting tensor, τ_v is the correlation time for the modulation of the ZFS with the activation energy E_v, and ω_s is the Larmor frequency of the Gd^{3+} electron spin.

$$\left(\frac{1}{T_{1e}}\right)^{ZFS} = \frac{1}{25}\Delta^2\tau_v\left\{4S(S+1) - 3\right\}\left(\frac{1}{1+\omega_S^2\tau_v^2} + \frac{4}{1+4\omega_S^2\tau_v^2}\right) \tag{10}$$

$$\left(\frac{1}{T_{2e}}\right)^{ZFS} = \Delta^2\tau_v\left[\frac{5.26}{1+0.372\omega_S^2\tau_v^2} + \frac{7.18}{1+1.24\omega_S\tau_v}\right] \tag{11}$$

$$\tau_V = \tau_V^{298}\exp\left\{\frac{E_V}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \tag{12}$$

The contribution arising from spin rotation is given by Eq. 13, where $\delta g_L{}^2$ is the deviation from the free electron g_L value and τ_R is the rotational correlation time.

$$\left(\frac{1}{T_{ie}}\right)^{SR} = \frac{\delta g_L^2}{9\tau_R} \qquad i = 1,2 \tag{13}$$

NMRD: The measured proton relaxivities [normalized to 1 mM Gd^{III} concentration] contain both inner-sphere and outer-sphere contributions (Eq.13).

$$r_1 = r_{lis} + r_{los} \tag{14}$$

The inner-sphere term is given by Eq. 15, where q is the number of inner-sphere water molecules.

$$r_{lis} = \frac{1}{1000}\times\frac{q}{55.55}\times\frac{1}{T_{1m}^H + \tau_m} \tag{15}$$

$$\frac{1}{T_{1m}{}^{H}} = \frac{2}{15}\left(\frac{\mu_o}{4\pi}\right)^2 \frac{\hbar^2\gamma_S^2\gamma_I^2}{r_{GdH}^6} S(S+1)\left[\frac{3\tau_{d1}}{1+\omega_I^2\tau_{d1}^2} + \frac{7\tau_{d2}}{1+\omega_S^2\tau_{d2}^2}\right] \qquad (16)$$

The longitudinal relaxation rate of inner-sphere protons, $1/T_{1m}{}^{H}$ can be expressed as in Eq. 16[31][32].

In Eq. 16, r_{GdH} is the effective distance between the Gd^{III} electron spin and the water protons, ω_I is the proton resonance frequency, and τ_{di} is given by Eq. 17.

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_R} + \frac{1}{T_{ie}} \qquad i = 1, 2 \qquad (17)$$

The outer-sphere contribution can be described by Eq. 18[25][33], where N_A is the Avogadro constant, and J_{os} is a spectral density function.

$$^{24}r_{os} = \frac{32N_A\pi}{405}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2\gamma_S^2\gamma_I^2}{a_{GdH}D_{GdH}} S(S+1)\left[3J_{os}(\omega_I, T_{1e}) + 7J_{os}(\omega_S, T_{2e})\right] \qquad (18)$$

$$J_{os}(\omega, T_{je}) = \mathrm{Re}\left[\frac{1 + \frac{1}{4}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{1/2}}{1 + \left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{1/2} + \frac{4}{9}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right) + \frac{1}{9}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{3/2}}\right]$$

$$j = 1, 2 \qquad (19)$$

For the temperature dependence of the diffusion coefficient for the diffusion of a water proton away from a Gd^{III} complex, D_{GdH}, we assume an exponential temperature dependence, with an activation energy E_{DGdH} (Eq. 20).

$$D_{GdH} = D_{GdH}^{298}\exp\left\{\frac{E_{DGdH}}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \qquad (20)$$

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